Exhibit 4

IN THE DISTRICT COURT OF CLEVELAND COUNTY
STATE OF OKLAHOMA

STATE OF OKLAHOMA, ex rel., MIKE HUNTER, ATTORNEY GENERAL OF OKLAHOMA,	
Plaintiff,	
vs.	**Case No. CJ-2017-816** **Judge Thad Balkman**
(1) PURDUE PHARMA L.P.; **(2) PURDUE PHARMA, INC.;** **(3) THE PURDUE FREDERICK COMPANY;** **(4) TEVA PHARMACEUTICALS USA, INC.;** **(5) CEPHALON, INC.;** **(6) JOHNSON & JOHNSON;** **(7) JANSSEN PHARMACEUTICALS, INC;** **(8) ORTHO-MCNEIL-JANSSEN PHARMACEUTICALS, INC., n/k/a JANSSEN PHARMACEUTICALS;** **(9) JANSSEN PHARMACEUTICA, INC., n/k/a JANSSEN PHARMACEUTICALS, INC.;** **(10) ALLERGAN, PLC, f/k/a ACTAVIS PLC, f/k/a ACTAVIS, INC., f/k/a WATSON PHARMACEUTICALS, INC.;** **(11) WATSON LABORATORIES, INC.;** **(12) ACTAVIS LLC; and** **(13) ACTAVIS PHARMA, INC., f/k/a WATSON PHARMA, INC.,**	**William C. Hetherington** **Special Discovery Master**
Defendants.	

DECLARATION OF RUSSELL K. PORTENOY, M.D

I, Russell K. Portenoy, M.D., declare as follows:

1. I am the Executive Director of the MJHS Institute for Innovation in Palliative Care and Chief Medical Officer of MJHS Hospice and Palliative Care. I am also a Professor of Neurology and Family and Social Medicine at the Albert Einstein College of Medicine. I received my Bachelor's Degree from Cornell University in 1976, where I was a member of *Phi Beta Kappa*.

I received my M.D., *cum laude*, conferred with Distinction in Neurology, from the University of Maryland School of Medicine in 1980, where I also received a Certificate in the Combined Accelerated Program in Psychiatry.

2. I completed my internship in Medicine at St. Luke's Hospital, New York, N.Y in 1981. I was a Resident in Neurology at the Albert Einstein College of Medicine in Bronx, N.Y., from July 1981- June 1984. I was appointed Chief Resident during my last year. From July 1984 to June 1985, I was a Fellow in Pain and Neuro-oncology at Memorial Sloan-Kettering Cancer Center. I became Assistant Professor of Neurology and Co-Director, Unified Pain Service, at the Albert Einstein College of Medicine in July 1985, and remained there until October 1987. I then returned to Memorial Sloan-Kettering Cancer Center as Director of Analgesic Studies on the Pain Service, which was in the Department of Neurology. I was concurrently appointed Assistant Professor of Neurology and Neuroscience, Cornell University Medical College. A decade later, in 1997, I was recruited to New York's Beth Israel Medical Center (now Mount Sinai Beth Israel) to create and chair the Department of Pain Medicine and Palliative Care. At the time of my departure from Memorial Sloan-Kettering Cancer Center, I was Co-Chief of the Pain and Palliative Care Service; I was also an Associate Professor of Neurology and Neuroscience at Cornell University Medical College. In 1997, I became Professor of Neurology at the Albert Einstein College of Medicine (co-appointment in the Department of Family and Social Medicine occurred in 2014). In 2003, while chairman of the Department of Pain Medicine and Palliative Care, I also assumed the position of Chief Medical Officer of the Jacob Perlow Hospice, which was then owned by Beth Israel Hospital. The Jacob Perlow Hospice was acquired by MJHS in 2010 and I became part-time Chief Medical Officer of MJHS Hospice and Palliative Care. I continued at Beth Israel Medical Center until 2014, when I joined MJHS on a full-time basis to found and direct the MJHS

Institute for Innovation in Palliative Care. From 2014 to the present, I have worked full-time for MJHS and have continued my professorship at the Albert Einstein College of Medicine.

3. I have agreed to cooperate with certain plaintiffs who have entered into settlement agreements with me dismissing me as a defendant in their cases ("Settling Plaintiffs"). Settling Plaintiffs agreed to dismiss me from their cases in exchange for my truthful cooperation. The proffer agreement with those Plaintiffs can be voided and the original lawsuits may be reinstated against me if my statements are recklessly and materially not truthful or accurate.

4. This declaration is based on personal knowledge, consisting of my own research and observations and my interactions with the opioid manufacturers who are defendants in this multidistrict lawsuit and in lawsuits across the country. This declaration includes statements describing how my views about opioid therapy and its marketing by the pharmaceutical companies have changed during the period between the mid-1980s and the first decade of the 2000s. At all times during this period, I espoused views that reflected my understanding of the complex problem of chronic pain and its management—views informed by my analysis of the medical literature that existed at the time and my extensive experience as a clinician using opioids to treat patients with chronic cancer pain and chronic non-cancer pain, and as an educator and researcher involved in opioid-related issues. Over the years, as evidence of increasing rates of opioid-related overdose and opioid abuse and addiction emerged, my views changed with the information that became available. My belief in the clinical benefits that are possible when appropriate patients with disabling pain that could not be relieved through conventional pharmacologic and non-pharmacologic therapies ('treatment refractory pain") are provided with long-term opioid therapy has consistently been held in good faith. This belief continues to the present. Given the information about adverse outcomes and risks that became available over time, however, I changed

my views about the need for caution in patient selection for opioid therapy and the ongoing need for careful risk assessment and management by physicians. I also came to believe that the opioid manufacturers should have tempered their positive messaging about opioids with a greater focus on risk, particularly as early signals of opioid risk emerged, and should have responded as evidence of increasing adverse effects mounted in a more aggressive manner to increase awareness and reduce inappropriate or risky prescribing.

My Early Experience with the use of Opioids to Treat Pain

5. I have been a clinician-investigator since the 1980s and my research with opioids began in parallel with my role as a physician treating patients with chronic pain. I have observed and treated numerous patients with chronic pain, including those with diverse non-cancer disorders and those with cancer or other life-limiting illnesses. While at Memorial Sloan Kettering Cancer Center, most of my experience with opioids involved the treatment of cancer pain. I developed a personal comfort level with prescribing opioids to treat pain and was involved in opioid clinical trials and studies of opioid pharmacokinetics. Beginning in the 1980s, during my fellowship, I perceived that opioids were seriously underused for cancer pain, particularly in the context of advanced illness.

6. Prior to, and then during the 1980s, opioids were disfavored for use in chronic, non-cancer pain because of concerns that patients using opioids would develop tolerance and physical dependence, and be at risk for abuse, misuse, addiction, and diversion.[1] Although opioids were more accepted for acute pain management in hospital settings, and for the management of chronic pain associated with advanced cancer or end-of-life care, my personal observations and my reading of the literature led me to the conclusion that these drugs were underused in these populations.

[1] Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. *Pain.* 1986;25:171-86.

My Early Writings Encouraging Acceptance of Opioid Therapy

7. In 1986, Kathleen M. Foley, M.D., and I wrote an article entitled "Chronic use of opioid analgesics in non-malignant pain: report of 38 cases."[2] This article reported that 24 of 38 patients who were treated with opioids experienced partial but acceptable or fully adequate pain relief. Two patients with a prior history of drug abuse developed problems. Psychosocial information was available from only 19 of the patients in this series. Aside from information about comorbid psychiatric diagnoses in six patients and the unverified statement that a minority of these 19 patients were employed, further information about the psychosocial functioning and employment of the patients in this group of cases could not be documented. This article was a retrospective case series describing anecdotal information about a highly selected group of patients. I recall that Dr. Foley and I wanted to write the paper to describe a phenomenon that we believed was under-appreciated by the medical community—the possibility of long-term pain relief from opioid therapy, without the development of tolerance leading to treatment failure and without the development of serious adverse effects, including drug abuse. We also wanted to use this description of cases as a starting point for a broad discussion of the clinical issues relevant to the appropriate use of these drugs. Our initial contribution to this discussion appeared in the Discussion section of the paper, which ended with our recommendation that opioid therapy be considered only after "all reasonable attempts at pain control have failed and persistent pain is the major impediment to improved function."[3] Contrary to how some drug companies later used this article, it was never intended as a report of high-quality evidence, or as support for broad adoption of opioid therapy; it was a description of anecdotal information accompanied by a brief narrative

[2] Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. *Pain.* 1986;25:171-86.
[3] Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. *Pain.* 1986;25:171-86.

review of the literature, and was intended to suggest that the role of long-term opioid therapy needed re-thinking, and more research, and that clinicians should not consider the approach to be contraindicated, but rather, worthy of consideration in the context of treatment refractory pain.

8. Professional societies and scientific journals helped establish pain medicine as a field of scientific research and clinical practice. As pain medicine became a bona fide discipline, national and international events took place, including educational symposia and meetings of experts to discuss advocacy, which were focused on the problem of cancer pain. These activities were grounded in growing evidence that cancer pain was inadequately managed, despite evidence that the regular use of opioids could be highly effective. In 1986, the World Health Organization published a very influential guideline called the "analgesic ladder" for the treatment of cancer pain. It recommended that opioids be used for chronic moderate or severe pain in populations with cancer. Specifically, the "ladder" approach recommended that non-opioid analgesics be used for mild pain; that opioids conventionally used for moderate pain (so-called "weak" opioids—of which codeine was the prototype) be used for mild pain that did not respond to a non-opioid or for pain that was generally moderate in severity; and that opioids conventionally used for severe pain (so-called "strong" opioids—of which morphine was the prototype) be used for moderate pain that did not respond to a "weak" opioid or for pain that was generally severe. In short, the "analgesic ladder" guideline was focused on cancer pain and recommended the use of a morphine-like opioid, such as oxycodone or fentanyl, whenever cancer pain did not respond to a "weak" opioid or was generally severe.

9. Between 1986 and 1994, I published 68 papers in the peer-reviewed literature and 101 review articles and book chapters about pain syndromes, mechanisms or management, and opioid therapy. In addition to the article that I wrote with Dr. Foley, there were 22 papers and

book chapters that included information about opioid therapy for chronic noncancer pain. In 1990, for example, I published a review article[4] in the Journal of Pain and Symptom Management that elaborated on the discussion that Dr. Foley and I wrote in our 1986 paper. It offered a set of guidelines based on experience (Table). The article's Conclusion included the following:

> …Selection criteria are entirely empirical, and careful consideration of the potential risks and benefits is needed in every case. Although the information available suggests that the risks are usually very small and that therapy can be discontinued if unsuccessful, the possibility that any individual may worsen, or indeed, develop addiction following the administration of opioids cannot be entirely excluded. The approach should be undertaken cautiously, and patients should be apprised of both its controversial nature and its potential advantages and disadvantages. Survey data suggest that a history of substance abuse may predispose to difficulty with the therapy, and its use in such patients should be considered only under the most extraordinary circumstances…"[6p.S58]

[4] Portenoy RK: Chronic opioid therapy in nonmalignant pain. J Pain Symptom Management 1990:5(1S):S46-S62.

This article's concluding statement notes that "therapy can be discontinued if unsuccessful". Implicit in this statement is the medical reality that opioid therapy cannot simply be stopped because of the risk of an acute withdrawal syndrome. Patients vary greatly in the extent to which they are able to taper and discontinue an opioid without the development of negative outcomes, including increased pain, psychological distress and the physiological manifestations of withdrawal.

Table (from Portenoy 1990)

1. Should be considered only after all other reasonable attempts at analgesia have failed.

2. A history of substance abuse should be viewed as a relative contraindication.

3.A single practitioner should take primary responsibility for treatment.

4. Patients should give informed consent before the start of therapy; points to be covered include recognition of the low risk of psychologic dependence as an outcome, potential for. cognitive impairment with the drug alone and in combination with sedative/hypnotics, and understanding by female patients that children born when the mother is on opioid maintenance therapy will likely be physically dependent at birth.

5. After drug selection, doses should be given on an around-the-clock basis; several weeks should be agreed upon as the period of initial dose titration, and although improvement in function should be continually stressed, all should agree to at least partial analgesia as the appropriate goal of therapy.

6. Failure to achieve at least partial analgesia at relatively low initial doses in the nontolerant patient raises questions about the potential treatability of the pain syndrome with opioids.

7. Emphasis should be given to attempts to capitalize on improved analgesia by gains in physical and social function.

8. In addition to the daily dose determined initially, patients should be permitted to escalate dose transiently on days of increased pain; two methods are acceptable: (a) Prescription of an additional 4-6 "rescue doses" to be taken as needed during the month. (b) Instruction that one or two extra doses may be taken on any day, but must be followed by an equal reduction of dose on subsequent days.

9. Most patients should be seen and drugs prescribed at least monthly. Patients should be assessed for the efficacy of treatment, adverse drug effects, and the appearance of either misuse or abuse of the drugs during each visit. The results of the assessment should be clearly documented in the medical record.

10. Exacerbations of pain not effectively treated by transient, small increases in dose are best managed in the hospital, where dose escalation, if appropriate, can be observed closely, and return to baseline doses can be accomplished in a controlled environment.

11. Evidence of drug hoarding, acquisition of drugs from other physicians, uncontrolled dose escalation, or other aberrant behaviors should be followed by tapering and discontinuation of opioid maintenance therapy.

10. In 1994, I authored a book chapter, *Opioid Therapy for Chronic Nonmalignant Pain: Current Status*.[5] In this chapter, I noted that the "traditional" view of opioids uniformly disfavored prescribing for chronic pain because of assumptions:

> According to conventional thinking, the initial response to an opioid drug may appear favorable, with partial analgesia and salutary mood changes, but adverse effects inevitably occur thereafter. It is assumed that the motivation to improve function will cease as mental clouding occurs and the belief takes hold that the drug can, by itself, return the patient to a normal life. Serious management problems are anticipated, including difficulty in discontinuing a problematic therapy and the development of drug seeking behavior induced by the desire to maintain analgesic effects, avoid withdrawal, and perpetuate reinforcing psychic effects. There is an implicit assumption that little separates these outcomes from the highly aberrant behaviors associated with addiction. If this portrayal were accurate, there would be compelling reasons to reject long-term opioid administration as a therapeutic strategy in all but the most desperate cases of chronic nonmalignant pain.

11. My writings aimed to describe these assumptions and evaluate them from the perspective of clinical experience and the literature that existed at the time. I repeatedly described the possibility of a favorable long-term outcome during opioid therapy while acknowledging the possibility of serious negative outcomes. In so doing, I defined and described the potential for adverse effects in terms of pharmacological toxicities, such as cognitive impairment, and abuse-related behaviors and phenomena. I emphasized that the development of abuse behaviors was complicated and emphasized the need for clinicians to assess and interpret these behaviors if they occurred. In my 1994 chapter, for example, I described a phenomenon that I then called *therapeutic dependence* and a phenomenon that had been labeled as *pseudoaddiction* in a 1989 article by Weissman and Haddox.[6] I noted that these phenomena could be characterized by behaviors such as hoarding, self-escalation of doses, or seeking out other prescribers. I described

[5] Opioid Therapy for Chronic Nonmalignant Pain: Current Status, 1 Progress in Pain Research & Management, 247-287 (H.L. Fields and J.C. Liebeskind eds., 1994).
[6] Weissman DE, Haddox JD, Opioid pseudoaddiction. Pain 1989;36(3):363-366.

therapeutic dependence as drug-seeking behavior in response to a threat of discontinuation of opioids and pseudoaddiction as drug-seeking behavior in response to untreated pain.

12. In all my writings, I acknowledged that the disease of addiction was a risk when opioids were used therapeutically. I stated in the 1994 chapter, as I did in many other writings during the 1980s and 1990s, that the disease of addiction would be "very unlikely" to develop when patients with chronic pain and no prior history of substance abuse were prescribed opioids and closely monitored. Although the evidence in support of this statement was scant in terms of the populations with chronic non-cancer pain, it was supported by large surveys of cancer patients receiving opioids for cancer pain. My conclusion was based on an analysis of the clinical literature at the time, which I acknowledged was very limited. In my 1990 article,[7] for example I stated the following:

> There is ample support for the proposition that opioids are inherently reinforcing drugs… The issue of iatrogenic addiction in pain patients thus focuses on the likelihood that these reinforcing properties are sufficient to produce addiction in patients who are not otherwise predisposed. In the absence of studies that directly evaluate this likelihood, influences about the risk of iatrogenic addiction can only be developed through information about the characteristics of pain patients and street addicts, and a review of epidemiologic surveys of addiction. Although these data are clearly inadequate to fully resolve this issue, together they provide a credible indication of the risk and clarify the questions that must be addressed in future surveys.

The credible indication of population-level risk could be defined as a distribution from very low risk to very high risk. The analysis in 1990 could not quantify this distribution into a set of probabilities, but it could indicate that there was in fact a proportion of patients with treatment-refractory chronic non-cancer pain that have a low enough risk to include opioids among the treatments that may be considered.

[7] Portenoy RK: Chronic opioid therapy in nonmalignant pain. J Pain Symptom Management 1990:5(1S):S46-S62.

Although many surveys during the decades since the 1990 article was written have largely supported the low risk of *de novo* addiction when patients with no prior history of substance abuse are prescribed opioids, this specific conclusion was never intended to substitute for a more complete description of abuse-related risks--drug abuse, addiction, overdose and diversion—which were also addressed in my writings. Moreover, although my work in the 1980s and 90s was intended to temper concerns that opioids inevitably lead to serious adverse consequences, the reassuring statements about addiction that I offered in these articles and chapters were made in conjunction with both explicit descriptions of the limitations in the scientific literature at the time and specific recommendations about the need for ongoing monitoring of, and response to, aberrant drug-related behaviors (#9 and #11 in the Table in paragraph 11). Finally, my early use of the term "street addicts" reinforced a dichotomy that I later appreciated as an oversimplification (if not unintentionally disparaging of those with the disease of addiction) of the complexity of addiction. The term "street" implied that addiction always presented in the context of other problems, like destitution, unemployability, psychiatric comorbidity. I realized later that this does not reflect the complexity of the disease and I stopped using the term "street addict" in later writings.

13. Opioid prescribing by both pain specialists and by primary care physicians started to increase in the mid-1990s. In my current lectures, I cite data based on a study of health care claims database that between 1987 and 2005 the prevalence of long-term opioid use increased by between 61% to 135%. The latter study was one of many showing that opioid prescribing, and specifically long-term prescribing, rose dramatically during these years, finally peaking around 2011. For a period of years after the increase in opioid prescribing began, there were no changes in the national indicators of opioid abuse or addiction. These turned out to be lagging indicators,

however. Although I do not have a clear recollection about when I realized that serious opioid-related adverse outcomes were increasing, I believe that I was aware of this phenomenon by the late 1990s and increasingly appreciated the seriousness of these problems throughout the 2000's and afterward.

14. On December 12, 1995, Purdue Pharma, L.P. introduced OxyContin, an extended-release version of oxycodone. During the subsequent years, the company aggressively marketed the drug. To my knowledge, no other company had previously promoted an opioid drug as aggressively, or encouraged the use of an opioid by non-specialists.

15. In 1996, I published another review article[8] on opioid therapy for noncancer pain. In this paper, I elaborated on the construct of "aberrant drug-related behaviors", which were depicted as a broad range of behaviors varying in severity and impact. With respect to the risk of addiction, I stated in this paper that:

> …these data suggest that the development of addiction results from an interaction between the inherent reinforcing properties of opioid drugs and predisposing psychological, social, and physiological factors that are presumably uncommon in the heterogeneous population of patients with chronic pain. Nonetheless, the data are limited and the prudent clinician must always consider the potential for addiction during the treatment of any patient. Opioid administration should be undertaken cautiously, and perhaps not at all in patients with a prior history of drug abuse, severe character pathology, or chaotic family relationships, all of which are suggested by clinical experience to be potential risk factors for problematic drug taking…

I again proposed guidelines in this paper that were similar to those in my 1990 paper (see Table in paragraph 11). The most important change was the recommendation to separately monitor four types of outcomes over time: "(a) comfort (degree of analgesia), (b) opioid-related side effects,

[8] Opioid Therapy for Chronic Nonmalignant Pain: A Review of the Critical Issues, J. Pain and Symptom Mgmt. 1996; 11(4):203-217

(c) functional status (physical and psychosocial), and (d) existence of aberrant drug-related behaviors."[9] I concluded the paper with the following:

> Controlled clinical trials of long-term opioid therapy are needed, but the lack of these trials should not exclude empirical treatment when medical judgment supports it and therapy is undertaken with appropriate monitoring. If treatment is offered, documentation in the medical record of pain, side effects, functional status, and drug-related behaviors must be ongoing and explicit.

16. I also stated that that the "psychological, social, and physiological factors" increasing the risk of addiction were "presumably uncommon in the heterogeneous population of patients with chronic pain." While this statement is true, it was not intended to compare the population with chronic pain and the general population. While I continue to believe that risk factors for addiction, particularly a past history of alcohol or drug abuse, are uncommon in all the varied subpopulations with chronic pain, this statement should have acknowledged that these risk factors are more common in some of these subpopulations, such as those with common musculoskeletal problems like low back pain, than in the population without chronic pain.

17. In 1996, a workgroup was formed by the American Academy of Pain Medicine and the American Pain Society for the purpose of creating a *Consensus Statement on the Use of Opioids for the Treatment of Chronic Pain.* The committee chair was Dr. J. David Haddox, who was hired by Purdue Pharma in 1999. I was not involved in the deliberations of the workgroup, but I recall that I was sent a draft of the consensus statement for my comments before it was presented to the respective organizations for approval and dissemination. I do not recall whether I made suggestions for modifications.

[9] Opioid Therapy for Chronic Nonmalignant Pain: A Review of the Critical Issues, J. Pain and Symptom Mgmt. 1996; 11(4):203-217, p. 211

18. Although the *Consensus Statement* noted that "It is imperative that this statement not be misconstrued as advocating the imprudent use of opioids," it presented a very favorable perspective, particularly as it related to risk, and implicitly promoted the wider use of opioids. In contrast to the lengthy articles and chapters that I authored, which attempted to correct what I perceived to be inaccurate negative information about opioid therapy while describing the limitations in the available studies and explicitly recommending careful patient selection and monitoring for aberrant drug-related behavior, the *Consensus Statement* was a very brief distillation of the positive view, without discussion of the limited science or explicit warnings concerning prescription practices. The *Consensus Statement* was endorsed by the two leading pain societies. I recall seeing it distributed at pain society meetings, and I believe that it was distributed to prescribers by representatives from the pharmaceutical companies that manufactured opioids.

19. On January 30 and 31, 2002, I was a panelist for the Food and Drug Administration Center for Drug Evaluation and Research Anesthetic and Life Support Drugs Advisory Committee Meeting. I understand that I was one of 5 panelists who had received some financial support from drug companies, out of 10 outside advisors.[10] At that meeting, I conveyed my impressions that opioids were under-used for chronic non-cancer pain, and further, the reason they were underused included lack of education concerning opioids. My view was also that opioids should be used more by primary care physicians, due to the scarcity of pain specialists. I also raised concern that both primary care and pain specialists lacked knowledge and adequate training for diagnosing and treating addiction.

[10] Peter Whoriskey, "The Prescription Painkiller Binge," Washington Post, December 31, 2012, p.A01.

20. In my early work, I advocated for greater use of opioids for chronic, non-cancer pain based on my understanding of the literature and my personal experience. My work put me in contact with the drug companies who are defendants in this litigation.

Financial Relationships with Defendants

21. Throughout my career, I accepted financial support from pharmaceutical companies. This support was of the type that was very common for successful physician academicians at the time. It included payments to me directly and payments to my institutional employer to support my academic and research activities. The payments to me were of two types: honoraria for speaking engagements and fees for consulting. The payments to my institution also were generally of two types: educational grants for developing and implementing academic conferences or writing or reviewing educational materials, and research grants in exchange for protocol-defined clinical research. The honoraria I received for speaking almost always involved conferences that provided continuing medical education credits. Sometimes these engagements were organized directly by the pharmaceutical company and sometimes they were organized by medical education companies contracted with the pharmaceutical companies. Consulting fees were paid by drug companies for work that usually involved attending an advisory board or assisting in the development of a research protocol. The educational grants to my institution could be provided directly by the companies or by the medical education companies that were contracted with pharmaceutical companies; over time, the role of the medical education companies increased. The conferences and the educational materials for which my institution received support from the drug companies almost always provided continuing medical education credits. The research grants received on my behalf by my institution were in exchange for scientific research.

22. Although I did not alter my positions in response to financial inducements from drug companies, I do understand they only funded activities that supported their interests. Throughout my career, I also received many grants from philanthropic foundations and a small number of research grants from government sources.

23. I did not exclusively seek funding for my work from opioid manufacturers, though these companies were a significant source of funding in some years. I also received both research funding and personal compensation from participation on advisory boards or consultation on research studies from drug companies that did not manufacturer opioids for activities identical to those that involved the opioid manufacturers.

24. The work for which I was compensated directly by drug companies mostly involved advisory boards. This work involved advising company scientists on the design of clinical studies involving pain. I also advised pharmaceutical company management, marketing executives, or researchers about best practices in pain management. My voice was one of many that the company representatives heard, and I have no evidence that the company subsequently followed the advice that they were offered.

25. Since I took my position at MJHS in 2014, I have not served on an advisory board, received consultation fees, or requested drug company funding for education. My organization participated in a multicenter study sponsored by AstraZeneca of a new drug for constipation in 2018, for we received less than $10,000. This study has now closed.

26. Based on my personal observations, the amount of funding provided by drug companies for the purpose of educating clinicians about drug abuse and addiction, and for the purpose of clinical research into the risk of abuse and addiction, was very limited between the 1980s and the 2000s. Prior to 1998, I do not recall any interactions with drug companies in which

funding for education or research about abuse or addiction was offered. In 1998, my colleagues and I presented a large professional education conference on pain and chemical dependency, and I recall that some of the opioid manufacturers provided educational grants to support the conference. Between 1998 and 2008, my colleagues and I presented another seven conferences of this type, and to the best of my recollection, the drug companies donated funds to support most of these conferences as well. Each of these donations was small relative to the overall cost of the conference and obviously very small relative to their marketing dollars.

27. I do not recall other interactions with a drug company during the 1980s and 1990s that included a request to develop education specifically about abuse or addiction, and I was not approached by any drug companies to discuss funding research into addiction risks. Based on my experience with the drug companies and my own observations of the medical literature, I believe that drug company research grants to researchers working in academic centers or health care facilities after a drug is approved for marketing almost always align with the company's interest in demonstrating the benefits of the drugs they manufacture, with the intention of publishing results that could yield higher sales in the future.

28. Over time, the drug companies appeared to increasingly outsource interaction about professional education to medical education vendors. I had numerous interactions with these vendors, all of which worked under contract with drug companies. At times, this involved an invitation to become the medical director of a continuing education conference about opioids, which might be proposed to a professional society as a 'satellite' conference; sometimes, I was asked to be a speaker at these conferences. At other times, a medical education vendor would ask me to participate in some other type of educational activity, such as production of a video or development of an educational tool. The vendors would contact experts and ask them to participate

in the writing of review articles for journals. For example, the article might be about the use of a drug in a specific population. On one occasion, I provided specific edits for an educational piece prepared by Springer Healthcare for Purdue, *PERFORM: Patient Evaluation Resources for Opioid Risk Management*. I removed statements that indicated opioid overdoses could only occur at certain doses. I also recommended the removal of a section endorsing the prescription of a low-dose opioid for a sample patient with high risk of current, untreated alcohol abuse on the grounds I did not consider it to be a description of a patient for whom opioids would be appropriate. I also recommended a change in terminology from "potentially addictive drugs" to "potentially abusable drugs." The phrase "potentially addictive drugs" implies that the only or most important risk is addiction and understates the potentially problematic behaviors, because in fact opioids are associated with a broad array of risks that are better characterized by the word "abuse." In retrospect, I believe that some of the original language in this educational piece, which I edited, could potentially encourage risky prescribing. This publication is available on the Purdue Pharma website. I also recall periodically receiving requests to author an article, typically a literature review, that would be submitted to a journal. Once published, an article could be distributed to prescribers. I recall that some of these offers to write review articles, which I did not pursue, included the help of a medical writer for assistance in drafting the paper.

29. Based on the interactions that I have had with medical education vendors, I believe that academicians who are provided with honoraria for producing or editing material must be vigilant to avoid messages that are not well supported or prudent, and are in the interest of the drug company, without a corresponding medical benefit for the patient. Although I cannot cite specific cases, my experience suggests that some of the work ostensibly created by academicians through interaction with medical education vendors reflects the work or the influence of drug companies.

30. Of the defendants and drugs in this case, I have worked on the following projects for Teva (Cephalon), Endo, Insys, Janssen, Mallinckrodt, and Purdue, as well as for Alpharma on its Kadian drug which is now distributed by Allergan. This is a list based on materials I had at my disposal, and does not reflect all work I have done:

a. From November 30 to December 1, 2006, I consulted for an advisory board for Alpharma for the drug Kadian, which is now distributed by Allergan, for which I was compensated $3,030.
b. In 2007, I worked on a multi-center clinical trial for Endo, for which my institution was compensated $8,880 upon completion.
c. On February 19, 2007, I participated in a seminar, "Breakthrough Pain Curriculum Development Workshop," for which I was compensated $3,000 by Advanced Strategies in Medicine. I believe this was financed ultimately by Cephalon, Inc. related to its drug, Fentora.
d. On May 15, 2007, I worked on an Advisory Board for Cephalon, Inc., concerning the drug Fentora, for which I was compensated $3,500.
e. On November 6, 2007, I presented a continuing medical education program, *Meet the Patients: Individualizing Therapy for Persistent and Breakthrough Pain*, for which I was compensated $2,000 by Advanced Strategies in Medicine, which was ultimately through Cephalon and related to its Fentora product.
f. In 2008, I entered into a consulting agreement with Insys for the purposes of product development, for which I was compensated at a rate of $500 per hour.
g. In 2008, I entered into an advisory board agreement with Endo for purposes of product development, for which I was compensated $2,500.
h. I contracted with Miller Medical Communications to present a continuing medical education program in Brooklyn, NY on October 30, 2009, sponsored by King Pharmaceuticals and Purdue Pharma entitled *When Opioids are Indicated for Chronic Pain: How to Optimize Therapeutic Outcomes and Minimize Risk*, for which I was compensated $2,000.
i. On December 16, 2009, I entered into a Master Health Care Professional Consultant Services Agreement with Purdue, running through December 31, 2011. That same day, I entered into a Statement of Work indicating the purpose was to provide expert opinion regarding new product opportunities, products currently under development, areas of unmet medical need, and the clinical application/implications of new Purdue products. I believe based on the date of this agreement, this concerned the launch of Purdue's Butrans product. I was compensated a total of $40,000 plus expenses for my work on this project.
j. On April 1, 2009, I participated in a Fentora Medical Scientific Advisory Board meeting for Cephalon.
k. On January 19, 2010, I chaired a meeting to develop a curriculum for a CME program sponsored by Endo and Janssen entitled *Balancing Chronic Pain Management and Rational Opioid Use for Primary Care Providers*.

l. On August 28, 2010, I participated in a Physician Advisory Board Meeting for Purdue.
m. In May 2010, I moderated an online program called *Medico-legal issues, clinical guidelines and opioid dose conversions* for the website Emergingsolutionsinpain.com, which was supported by Cephalon, Endo, and Purdue, and for which I received $2,000.
n. On February 5, 2010, I entered into a consulting agreement with Mallinckrodt to advise on pain and addiction medicine, for which I was paid $3,500.
o. On November 15, 2010, I entered into an Educational Preceptorship Agreement with Mallinckrodt for the purpose of educating Mallinckrodt's medical science liaisons on clinical practice, for which I was paid $8,000
p. On February 11, 2011, I entered into an advisory board agreement with Cephalon, Inc.

31. In 2003, I co-authored a research paper that was published in a prestigious journal and described the results of a Purdue-supported study of OxyContin in diabetic neuropathy. One of my co-authors, Patricia Richards, was a Purdue employee.[11] I believe that Purdue distributed this study to prescribers. The study was a randomized, double-blind, placebo-controlled multicenter study that measured pain intensity changes over six weeks. It found that OxyContin was efficacious relative to placebo, and that 80 of 82 subjects reported adverse events, compared with 52 of 77 placebo patients. The study also found that "[n]o significant differences were observed between CR oxycodone and placebo groups in … physical functioning, general health, and mental health[.]" This type of controlled clinical trial provides what is considered to be high-quality evidence. This evidence is needed by clinicians to confirm that the drugs they select can be efficacious when they are treating patients. However, these studies recruit patients based on strict inclusion criteria, and consequently, the results may or may not be immediately transferable to practice. In studies of opioids, the patients who are recruited are carefully selected and may not be representative of the overall population with pain; moreover, the duration of study is short compared to the patients treated in practice, and study patients are carefully monitored while they

[11] Gimbel, J. S., Richards, P., & Portenoy, R. K. (2003). Controlled-release oxycodone for pain in diabetic neuropathy A randomized controlled trial. *Neurology*, *60*(6), 927-934.

are receiving the study drugs. Clinical practice needs randomized controlled studies to provide an evidence base for patient care, but clinical guidelines are not created solely from the data acquired in these studies. It is my belief that this understanding of the role played by high-quality randomized clinical trials, i.e., necessary to establish the potential for efficacy but insufficient for clinical guidelines that must consider a patient population not represented in the study and patterns of drug use that are not specifically tested, is widely accepted by clinicians and investigators, and would be considered common knowledge in the pharmaceutical industry.

32. In 2004, I edited a publication distributed by Endo Pharmaceuticals, *Understanding Your Pain: Taking Oral Opioid Analgesics*. This publication included a Question and Answer section designed for patients and included statements about addiction and dose increases. I do not recall perceiving that any of these statements were misleading at the time, but now agree that they were excessively brief and lacked context and appropriate warnings. For example, the pamphlet stated, "taking opioids as prescribed for pain relief is not addiction." Although this brief comment is accurate in the sense that the use of an opioid as directed can never define addiction (addiction requires compulsive drug use, loss of control, craving and continued use despite harm), it greatly oversimplifies reality. Addiction can exist while pain is experienced. The statement that "addiction to an opioid would mean that your pain has gone away but you still take the medicine regularly" is incomplete because some patients will continue to take the drug, as instructed, when pain is gone in order to prevent recurrence, and some will abuse the drug but not fulfill the criteria for a diagnosis of addiction. The statement that "dose can be increased or other medicines can be added. You won't 'run out' of pain relief" is true in the sense that there are options should a patient taking an opioid report that pain is increasing despite treatment, it lacks a warning—opioid dose escalation has increased pharmacological risks, like the risk of respiratory problems, and

overall, may produce risks that outweigh the benefits or reflect problems developing with the drug itself, including the possibility of addiction. Together, the statements in this pamphlet project a positive view of opioid therapy and with the benefit of hindsight lacked context and warnings, and may have induced a false sense of security. A responsible company should disclose relevant risks when communicating with the public, and although I did not perceive the statements in this pamphlet as deficient in 2004, the risks associated with opioid abuse and addiction were known at that time, and, in retrospect, the language in the pamphlet should have included more balanced information about the risks.

33. In 2007, I published an article used by Purdue and cited in the OxyContin drug label,[12] which described a retrospective analysis of data acquired during long-term OxyContin treatment of patients who successfully completed a controlled trial of OxyContin and consented to participate in a so-called extension protocol. The data collected from these patients were entered into a registry that could be analyzed. The data were limited, originated during open-label treatment, and there was no comparison group. Adverse event reports obtained during this registry study were included in the prescribing information. The patients reported in the study took OxyContin for a mean of 541 days. During the treatment period, they were prescribed a broad range of doses and were permitted to take supplemental medications for "breakthrough" pain.[13] The study concluded that pain relief was maintained over time for many of the patients. The need for high doses and use of breakthrough pain medications may indicate that the outcomes—pain relief and function—of some of the patients may not have been adequate, or as good as would have been obtained with alternative treatment, but the study was not designed to answer this question.

[12] "Long-term use of controlled-release oxycodone for noncancer pain: results of a –year registry study." Clin. J. Pain. 2007; 23:287-99

[13] Two 80 mg tablets, at a 1.5:1 conversion ratio.

34. I believe that, over the years, some Defendant drug companies have used my work to promote opioids by referencing the positive statements that I made repeatedly without providing the background, analysis of the literature, and cautions that accompanied these positive statements. For example, in 2001, Purdue cited my work to describe as "myths" the propositions that opioids will routinely cause addiction, that motor skills and/or driving skills are significantly impaired, that opioids lead to significant cognitive impairment, that they are absolutely contraindicated in persons with addictive disorders, that doses will require continual escalation, and that adequate pain control now will lead to poor response later. Although information about abuse and addiction appears in the presentation that included reference to "myths", the decision to label these phenomena as 'myths' was imprudent. The professionals in Purdue would have known that these risks still existed, and that messages about 'myths' could potentially be construed as contradicting the reality of these risks. I believe that each of these statements require additional warnings to translate to good clinical practice. Patients who have risk factors for the development of an active addiction require a careful assessment to evaluate potential benefits against risks to decide whether to try an opioid, and vigilant monitoring is needed if opioids are to be used at all. Additionally, patients should be cautioned about the risks of impaired cognitive function. While I continue to believe that these risks were overstated in the past and helped generate a stigma against opioids, it is evident that good medical practice requires that they be taken more seriously than Purdue's language suggested. A 1997 Purdue brochure likewise cited me saying that opioid therapy was "appropriate, safe, and effective on a long-term basis for selected patients," then presents questions and answers that describe a very positive view of this therapy. It indicates that the risk of addiction is <1%, although this is an inaccurate interpretation of data (see paragraph 40) and does not provide appropriate warnings about other types of risks; it also does not indicate that opioids should be

tried after other reasonable efforts at pain management have been unsuccessful, suggesting instead that opioids could be used before potentially safer non-opioid alternatives.

35. Drug companies are a major source of research funding and have the ability to influence study proposals. In my opinion, it is clear that drug company research grants provided to academicians for studies of approved drugs generally fund studies that aim to identify or confirm benefits that would be helpful in marketing. Similarly, I believe that the drug companies distribute honoraria, fees and grants in a way that elevates specific messages, and messengers, that agree with their preferred messaging. Although I personally was never influenced to say things I did not believe, it is true that the drug companies provided me with many opportunities to express my views, and they used the positive statements that I made about opioids to portray opioid treatment as safe and effective without the accompanying discussion of risk that I included in the papers, chapters, and lectures I produced beginning in the 1980s.

36. My work was intended to disabuse clinicians of a bias against opioids by describing the literature as it existed then and the favorable outcomes that I and others were seeing in varied subgroups of patients, and by providing guidelines for treatment that included careful patient selection and vigilant monitoring of drug-related outcomes over time. I believe that the drug companies created material that narrowly focused on the potential for safe and effective treatment of chronic noncancer pain, some of which was attributed to my work, but failed to include an adequate and balanced discussion of the limitations in the relevant science and the risks as they were then known.

Work with Pain Societies

37. During my career, I was also involved with several medical and advocacy societies in which I interacted with some of the drug companies who are defendants in this lawsuit. I was

a board member of the American Pain Society (APS) from 1989-1992, President from 1998-1999, and a board member of the American Pain Foundation from 2000-2012.

38. The American Pain Foundation (APF) was created by several prominent members of the APS for the purpose of responding to the need for public education and advocacy about pain. During my time on the board, APF was funded mostly through pharmaceutical company grants. This was a concern for the APF board for many years. Ultimately, APF was not able to continue after drug companies withdrew funding. During my time with the APF, I helped edit its major publication, a monograph for the public on pain management. The APF staff pursued projects focused on pain management, including opioid management, and did not focus on opioid abuse or addiction. APF undertook a series of projects that were intended to improve pain management and access to pain treatments. It did not pursue activities focused on the rising problems of opioid abuse and overdose. Although management and board members were never induced to create specific messages or change a message that was proposed as part of any project, it is true that dependence on drug company grants influenced the types of projects that could be pursued. Given the lack of funding for projects that would promote nonopioid and non-drug therapies, these projects were not pursued by APF. I believe the dependence on funding from opioid manufacturers may have constrained the ability of APF to take positions that would be disadvantageous to industry.

39. In 2009, I served on a panel of the American Pain Society and the American Academy of Pain Medicine to develop what became the *Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain* (the "2009 APS/AAPM Guidelines"). The methodology employed to create this guideline reflects best practices in the creation of so-called 'evidence-based guidelines' and was overseen by the Oregon Evidence-based Practice Center at

the Oregon Health and Science University. The methodology included a systematic review of the available literature. This systematic review included an analysis of the quality of evidence that the different publications offered, a designation based on the type of study (e.g., randomized controlled trials are higher quality evidence than surveys) and the rigor of the methodology employed by the studies. This review of the literature and its quality was evaluated by an expert panel, which worked with the organizers to create a first draft of guideline statements. Of the twenty-one panelists participating in this effort, fourteen had received fees or research funding from one or more of Endo, Janssen, Mallinckrodt, Purdue, and Teva. The guideline statements were accepted, revised or eliminated by the panel using an approach to consensus-building known as the Delphi method. The guidelines were then categorized by whether the recommendation being made was "strong" or "weak" based on the quality of the available studies (high, medium, or low-quality) and the discussion by the panelists. The 2009 APS/AAPM Guidelines include a number of the recommendations acknowledged to be based on low-quality evidence, including the following:

a. "Before initiating COT [chronic opioid therapy], clinicians should conduct a history, physical examination and appropriate testing, including an assessment or risk of substance abuse, misuse, or addiction;
b. "Clinicians may consider a trial of COT as an option if CNCP [chronic, non-cancer pain] is moderate or severe, pain is having an adverse impact on function or quality of life, and potential therapeutic benefits outweigh or are likely to outweigh potential harms."
c. "A benefit-to-harm evaluation including a history, physical examination, and appropriate diagnostic testing, should be performed and documented before and on an ongoing basis during COT."
d. "When starting COT, informed consent should be obtained. A continuing discussion with the patient regarding COT should include goals, expectations, potential risks, and alternatives to COT."
e. "Clinicians and patients should regard initial treatment with opioids as a therapeutic trial to determine whether COT is appropriate."
f. "Opioid selection, initial dosing, and titration should be individualized according to the patient's health status, previous exposure to opioids, attainment of therapeutic goals, and predicted or observed harms."
g. "Clinicians should reassess patients on COT periodically and as warranted by changing circumstances. Monitoring should include documentation of pain

intensity and level of functioning, assessments of progress toward achieving therapeutic goals, presence of adverse events, and adherence to prescribed therapies."

h. "In patients on COT for patients who are at high risk or who have engaged in aberrant drug-related behaviors, clinicians should periodically obtain urine drug screens or other information to confirm adherence to the COT plan of care."
i. "Clinicians may consider COT for patients with CNCP and a history of drug abuse, psychiatric issues, or serious aberrant drug-related behaviors only if they are able to implement more frequent and stringent monitoring parameters. In such situations, clinicians should strongly consider consultation with a mental health or addiction specialist."
j. "Clinicians should evaluate patients engaging in aberrant drug-related behaviors for appropriateness of COT or need for restructuring of therapy, referral for assistance in management, or discontinuation of COT."
k. "When repeated dose escalations occur in patients on COT, clinicians should evaluate potential causes and reassess benefits relative to harms."
l. "In patients who require relatively high doses of COT, clinicians should evaluate for unique opioid-related adverse effects, changes in health status, and adherence to the COT treatment plan on an ongoing basis, and consider more frequent follow-up visits."
m. "Clinicians should taper or wean patients off of COT who engage in repeated aberrant drug-related behaviors or drug abuse/diversion, experience no progress toward meeting therapeutic goals, or experience intolerable adverse effects."
n. "Clinicians should counsel patients on COT about transient or lasting cognitive impairment that may affect driving and work safety. Patients should be counseled not to drive or engage in potentially dangerous activities when impaired or if they describe or demonstrate signs of impairment."
o. "Patients on COT should identify a clinician who accepts primary responsibility for their overall medical care. This clinician may or may not prescribe COT, but should coordinate consultation and communication among all clinicians involved in the patient's care."
p. "Clinicians should counsel women of childbearing potential about the risks and benefits of COT during pregnancy and after delivery. Clinicians should encourage minimal or no use of COT during pregnancy, unless potential benefits outweigh risks. If COT is used during pregnancy, clinicians should be prepared to anticipate and manage risks to the patient and newborn."

40. I understand that pharmaceutical companies assisted in publicizing these guidelines and relied on them in marketing and publications. In any discussions of or reliance on the 2009 APS/AAPM Guidelines, it would be important to disclose not only the substance of the Guidelines' recommendations, but the strength of the evidence on which they were based. If the fact that many of the recommendations lacked support from high-quality studies is not known, a reader could

assume that adherence to the guidelines ensures a high likelihood of effective and safe therapy; knowing that the best evidence supporting a guideline is actually lower quality evidence would likely encourage greater caution in patient selection and management. In addition, in hindsight, the Guidelines also lacked some important information. They did not describe how to proceed with a particularly high level of caution, with reassessment and monitoring, if patients appear to require repeated dose escalations to maintain effects. They did not describe non-opioid methods for dealing with residual pain after partial pain reduction is achieved. They did not include instructions on how to taper patients off opioids, or mention the time and difficulty involved in doing so. They also did not describe an approach to the diagnosis of addiction or provide specific instructions should the patients' drug-related behavior suggest an addictive pattern. In retrospect, given the information that was continuing to emerge about the rising rates of adverse opioid effects, these points should have been considered as potential priorities for inclusion in the Guidelines by the expert panel and subjected to the review process that culminated in the language adopted. With the benefit of hindsight, additional important information about risk management should have been included.

Concerns About Opioid Prescribing

41. Although my work has consistently discussed both the risks and benefits of opioids I have acknowledged that my teaching and writing at various times emphasized the potential benefits (that I believe could be achieved by a subgroup of patients), and deemphasized the risks that are always present when opioids are administered. I believe that drug companies used my work to provide content and expert support for a strongly positive message about opioids, and in much of the material produced by drug companies, the content lacked context and warnings, and

in so doing, presented a message that lacked balance. The effect was to promote opioid therapy to prescribers.

42. Opioid therapy is an appropriate first-line therapy for some types of moderate to severe acute pain, such as postoperative and post-traumatic pain, and moderate to severe chronic pain associated with active cancer or other advanced chronic illness and breakthrough pain in opioid-treated patients with serious illness. When discussing the role of this therapy for patients with "chronic nonmalignant pain," the terminology may be confusing. Patients with advanced illnesses other than cancer could be said to have chronic nonmalignant pain, but the clinical approach to these populations mirrors those with cancer. The context for discussion about the risk of long-term opioid therapy is their use for those patients with chronic noncancer pain" or "chronic nonmalignant pain" that is not linked to life-limiting diseases—syndromes such as low back pain, neck pain and headache. For these syndromes, opioid therapy is rarely a first-line therapy, a point that has appeared in my writings since 1986. As a matter of clinical practice, use of an opioid in a patient presenting with one of the common forms of chronic pain should generally be delayed because other approaches may be able to provide analgesia with fewer side effects and risks. Similarly, some patients who may otherwise be candidates for opioid therapy have a medical comorbidity that increases the risk of using opioids and justifies withholding the approach.

43. In 2011 and in 2012, I publicly acknowledged that my earlier work "left evidence behind" in an effort to destigmatize opioids. In my writings, I cited a 1980 letter to the editor of the New England Journal of Medicine describing a review of medical charts (the "Porter & Jick" letter)[14] as a piece of epidemiologic evidence that was reassuring with respect to the risk of addiction. This piece of research was very limited; its retrospective design, meager description of

[14] Porter, J., & Jick, H. (1980). Addiction rare in patients treated with narcotics. The New England journal of medicine, 302(2), 123.

clinical information about the patients included, inability to provide confirmation of future outcomes, and lack of sophisticated statistical analysis were all study limitations that warranted the editors' decision to permit publication only as a letter and not as a full article. Equally important, interpretation and the generalizability of the data presented must be understood in terms of the question being asked ("What is the incidence of addiction after inpatient exposure to an opioid"). Management of pain in a hospital is very different than management of pain in the community, and the data in this Letter were not relevant to the important question ("What is the incidence of addiction in a specific patient population during opioid treatment that continues for years?"). I was aware of these limitations but my intent at the time was to include all of the epidemiologic literature available, and this amounted to a very small number of papers. My writings included reference to all of these citations and I attempted to provide context by adding explanatory information ("It must be emphasized, however, that neither this observation, nor any of the data described previously, directly assesses the risk of addiction among chronic nonmalignant pain patients administered opioids for prolonged periods."). In retrospect, the inclusion of data from studies (particularly the Porter & Jick letter) that reflected clinical scenarios so removed from the scenario of interest (long-term treatment of chronic pain patients) should not have been used to support the conclusion that opioid risk is very low. Moreover, the statistic from the Porter & Jick letter—an addiction rate of <1% following short-term inpatient opioid exposure—should not have been used by the pharmaceutical industry to indicate the addiction rate associated with chronic pain treatment. That statistic should not have been presented unless accompanied by discussion of the limitations and context for the study from which the data originated. In 2012, I was profiled by the *Wall Street Journal*,[15] where I also stated that evidence

[15] Thomas Catan and Evan Perez, Á Pain-Drug Champion Has Second Thoughts," *Wall Street Journal* (Dec. 17, 2012).

of drug overdoses led me to reevaluate much of what I had said about patient risk, including reliance on the Porter & Jick article.

44. I also understand that promotion of pseudoaddiction became problematic after the term was introduced by Weissman and Haddox in 1989.[16] I believe that the term was meant to be applied to patients without the disease of addiction who engage in less serious types of aberrant behavior (such as complaints, frequent calls, demands, and the like) when unrelieved pain is associated with anxiety and even desperation. The term should not have been used to describe more serious behaviors, such as "doctor shopping". Moreover, the reality that unrelieved pain can promote aberrant behaviors should never be used to avoid the diagnoses of 'abuse' or 'addiction' when these are appropriate, and should never immediately justify higher doses of an opioid as a solution. There is a risk that clinicians who learn about pseudoaddiction may be less vigilant about identifying abuse and addiction and may default to more opioids as treatment instead of management determined by careful reassessment and proper diagnosis. In hindsight, the dissemination of the concept of 'pseudoaddiction' without clear messaging about the appropriate response to aberrant behaviors could have led prescribers to continue opioid therapy when it should be tapered or stopped.

45. I believe that my work was, over a period of years, used by drug companies to create positive messaging about opioid therapy without a concurrent disclosure and discussion of risks. This was done as part of marketing. Statements that I made at various times which portrayed the risk of addiction among patients with no prior history of addiction who are prescribed opioids for chronic pain as rare or very low should have been presented with explanation and cautions, as I tried to do in my work. Even if the de novo appearance of iatrogenic addiction in patients with

[16] Weissman DE, Haddox JD, Opioid pseudoaddiction. Pain 1989;36(3):363-366.

no history of alcohol or drug abuse, particularly those who are older and lack other risk factors, is rare, messaging about this risk should point out that even rare events will occur if the prevalence of use increases very dramatically Messaging should always note that addiction is a disease, and is only one of a number of risks that must be considered when selecting patients for treatment or monitoring them over time; these risks also include unintended overdose, drug abuse behaviors, and diversion. This highlights the necessity of monitoring for aberrant behaviors and having the skills necessary to identify abuse and addiction, if they were to occur. Identifying and effectively monitoring these aberrant behaviors requires a level of clinical skill and a commitment to monitoring that may not be common among primary care physicians. I believe that the drug companies portrayed an excessively positive message about opioids, which included the use of some of my work, and when serious abuse-related outcomes appeared nationally, they did not promptly modify these messages so that they included more discussion about the risks presented.

46. I have long believed that direct-to-consumer advertising in the opioid context is a terrible idea, and at one point, I advised representatives of Janssen against a direct-to-consumer campaign; this idea was not pursued. Patients in pain are often desperate for help, and they are likely to be strongly influenced by advertising. Exposed to positive messages about opioids, they may try to push their physicians into opioid prescribing. The decision to offer a trial of this therapy is challenging and requires the ability to assess patients appropriately and manage therapy. If clinical decision making is influenced by patients attempting to advocate for themselves using messages they see in advertising, direct-to-consumer advertising could result in more prescribing by ill-prepared physicians and increase the potential for adverse outcomes. This concern about advertising also extends to primary care physicians themselves. I recall that I was surprised when I first saw a full-page color advertisement for Oxycontin in a general medical journal. Colleagues

of mine, specialists in pain management, to whom I spoke at the time also expressed surprise. This surprise reflected the sense that a line had been crossed, that opioids—drugs that had been considered too risky to even consider for the vast majority of patients with chronic pain—were being promoted to primary care physicians in the same manner as drugs without any of this history. This was not education, but rather pure promotion, and I recall that my surprise was accompanied by some concern about the potential for increasing inappropriate prescribing through this approach.

47. I believe that drug companies disseminated the results of positive clinical studies of opioid drugs without providing important information that would allow prescribers to understand the extent to which a trial relates to clinical practice. Clinical trials that provide high-quality evidence of efficacy are typically called 'explanatory;' in contrast to so-called 'pragmatic' trials. Explanatory trials of opioids include those randomized, placebo-controlled studies that show efficacy in a particular type of pain population. These studies show that a drug can provide analgesia, but they must be interpreted carefully with respect to the exigencies encountered in practice. They exclude patients with a history of drug abuse or addiction and study patients for a relatively short period of time. Drug companies often distribute publications that describe explanatory trials, and I believe that they do not create messaging at the same time that helps physicians understand the connection to practice. For example, physicians may not know that the patients recruited for explanatory trials have no history of substance abuse or that treatment for 6-12 weeks does not provide evidence of long-term effectiveness.

48. The practice of "enriched enrollment," which is a type of clinical trial design often used in pivotal trials supporting FDA approval of an opioid, exemplifies how these explanatory trials do not provide the type of information about risk that is needed in clinical practice. In these

studies, there is an initial open-label phase to select patients who respond to a drug; this is then followed by a double-blind phase to determine whether these responders continue to have benefit from the drug when their effects are compared with a placebo treatment. Patients with addiction risk are typically screened out of the open-label phase, and patients who do not do well during the open-label phase are also dropped from the double-blind phase. Enriched enrollment studies are therefore designed only to see if a drug has a primary outcome, like analgesia, that exceeds placebo in a selected group of favored patients. It is not designed to assess outcomes in the heterogeneous population of patients seeking care in clinical practice, nor is it designed to assess long-term risks. Although drug companies should include documentation of evidence from explanatory trials in their labels, they should be cautious in pointing to these studies as proof of a drug's safety in real world conditions.[17]

Conclusion

49. Based on my personal experience with the drug manufacturers and their vendors, I believe they regularly conveyed information to prescribers that stated or implied that opioid drugs were useful for the treatment of chronic noncancer pain, and failed to convey adequate information about both the limitations of the available data in this population and the potential for serious adverse outcomes in a subset of patients. Opioid manufacturers overstated the benefits of chronic opioid therapy by extrapolating from limited data to suggest that opioids were likely to be better suited for more patients, and by understating the risks of opioids, particularly the risk of abuse, addiction and unintended overdose among the chronic pain population. These unbalanced communications from drug manufacturers and their vendors encouraged opioid prescribing. One

[17] I conveyed this point at the April 1, 2009 Fentora medical Scientific Advisory Board Meeting, where I stated "[o]verall rates of abuse were low in the clinical studies, most notably the long-term safety study. However, this may not apply to real world rates given that the patients were selected to enter the study based on exclusion of patients at high risk."

result was prescribing to patients who were inappropriate for chronic opioid therapy. Another was prescribing by physicians who lacked the skills in assessment and management of adverse outcomes when they occurred. In some of the material created by the manufacturers, my work was summarized in a manner that did not include the caveats or analysis, or the clinical recommendations that reflected my desire to destigmatize the therapy without losing the message that serious adverse consequences are possible. Prescribing of opioids on a large scale to patients who were poor or inappropriate candidates for therapy, prescribing in a manner that did not reflect risk assessment, and prescribing without appreciation of the skills needed to monitor abuse-related outcomes or to discontinue therapy if needed all contributed to the rising incidence of drug addiction and overdoses. Addiction and overdoses were certainly known risks, since they were key in discouraging the use of opioids in clinical practice at the start of my career.

I declare under penalty of perjury that the foregoing is true and correct. This declaration was executed in NEW YORK, N.Y., on JANUARY 17, 2019.

Russell K. Portenoy, M.D.